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(54) Title: PROSTAGLANDIN PHARMACEUTICAL COMPOSITIONS

(57) Abstract

Compounds of the general formula $A–X_1–NO_2$, or their pharmaceutical compositions, wherein A contains a prostaglandin residue, X_1 is a bivalent connecting bridge.

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PROSTAGLANDIN PHARMACEUTICAL COMPOSITIONS

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The present invention relates to drugs to be used in male impotence.

In particular it relates to drugs which are used at lower but equally effective doses than those commonly used for the treatment of said therapy, and combined with fewer side effects, in particular as far as the absence of hypotension and algogenic activity is concerned.

It is well known in the art that the available therapies for treating male impotence are based on different approaches depending on the aetiology.

In the case of impotence due to endocrine causes treatment with testosterone is used.

In the case of impotence due to vascular alterations, or following from some neurological alterations, it is used an intracavernous injection of vasoactive compounds made by the patient himself before sexual intercourse. This method of administration allows a local pharmacological activity and reduces to a minimum any interference with the other vascular areas of the body which could lead to severe side effects

including vasodilation and hypotension. The drugs more frequently used with said method include the association papaverine-phentolamine and Prostaglandin E_1 (PGE_1). This is a useful approach from the therapeutic point of view, but it has the disadvantage to presenting side effects. In fact, papaverine induces local fibrosis, prolonged erections and hepatic alterations; Prostaglandin E_1 induces pain in 20% of cases and prolonged erections in 1-2% of cases. PGE_1 is anyhow at the moment the drug most used for this type of therapy.

Besides clinical drug treatments, are well known in the art the use of prostheses and mechanical devices.

At the present time, the available drugs solve the problem only in a limited number of cases. Research is being made on the basis of various hypothesis. However, the drugs which have been proposed up to now are less active than prostaglandin-based drugs.

It was felt the need to have drugs as effective in the treatment of impotence as least as those based on prostaglandin but without presenting the side effects possessed by said known drugs as described above.

It has been surprisingly and unexpectedly found a class of drugs as herein below defined which has an improved activity than prostaglandin and the advantage of being used

at lower doses with less side effects, in particular it does not cause any hypotension or algogenic activity.

It is an object of the invention the compounds, or their compositions having the general formula

$$A - X_1 - NO_2 \quad (I)$$

for use as medicaments, in particular as drugs for the treatment of impotence, wherein:

$A = R(CR_aR_bO)_u(COX)_t$ (II)

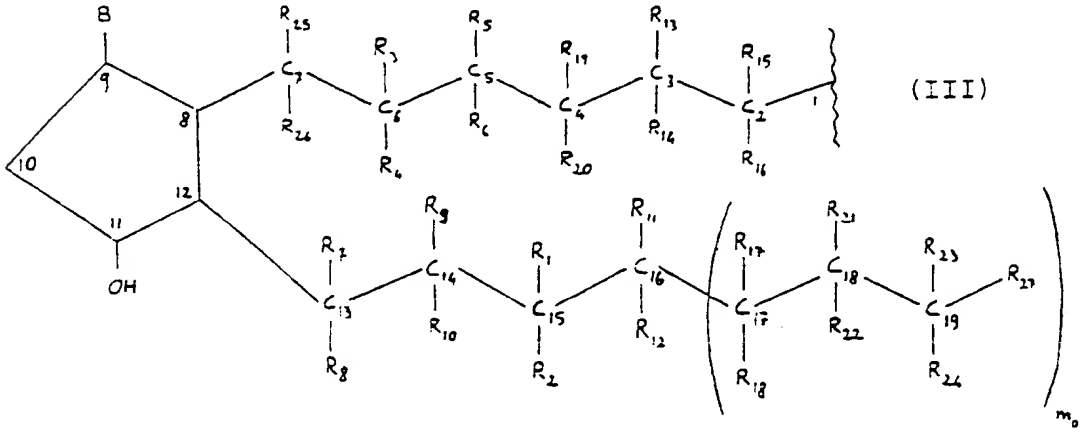
wherein:

t and u are integers and are equal to 0 or 1;

X = O, NH, NR_{1c} wherein R_{1c} is a linear or branched alkyl having from 1 to 10 carbon atoms;

R_a and R_b, equal or different from each other, are H, C_1-C_3 alkyl;

R is a radical having the following formula:



(III)

where m_o is an integer and can have a value of 0 or 1;

where the meaning of the various substituents of formula III is as it follows :

<u>when t = 1, u = 0 and m_o = 1</u>:

R_1 = H; an alkyl having from 1 to 6 carbon atoms, preferably from 1 to 3, or a free valence;

R_2 = OH; O- such as to form with R_1, when R_1 is a free valence, and with the carbon atom at position 15, a group C=O;

R_3, R_4, equal or different one from the other, are equal to R_1, or one of them is a bond O-, and the other is a free valence so that with the carbon atom C_6 they form a group C=O;

R_5, R_6, equal or different one from the other, are equal to R_1, in particular when both R_5 and R_3 are each a free valence, R_5 and R_3 form a double bond between C_5 and C_6;

R_7, R_8, R_9, R_{10}, equal or different one from the other, have the same meaning of R_1; when R_7 or R_9, and at the same time R_8 or R_{10} are each a free valence, there is a double bond between C_{13} and C_{14};

R_{11} = R_1;

R_{12} = R_{11} or OH;

R_{13}, R_{14}, R_{15}, R_{16}, equal or different one from the other, are equal to R_1; when R_{13} or R_{15}, and at the same time R_{14} or R_{16}, are

each a free valence, there is a double bond between C_3 and C_2;

R_{17}, R_{18}, equal or different one from the other, are equal to R_1;

R_{19}, R_{20}, equal or different one from the other, are equal to R_1; when R_6 or R_5 is a free valence, and at the same time R_{19} or R_{20} is a free valence, there is a double bond between C_4 and C_5;

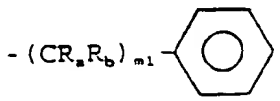
R_{21}, R_{22}, R_{23}, R_{24}, equal or different one from the other, are equal to R_1;

R_{25}, R_{26}, equal or different one from the other, are equal to R_1, but both R_{25} and R_{26} cannot be a free valence;

R_{27} is a linear or whenever possible branched alkyl having from one to six carbon atoms;

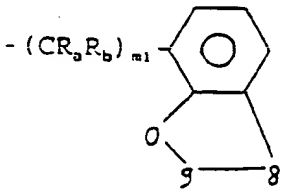
B is equal to the group O= (a keto group with the carbon atom at position 9 of the prostaglandin molecule), OH, or -O-;

when no aliphatic chain C_7-C_2 is found attached at position 8, in its place there is the alkylaromatic residue:



(IV)

wich is bound to formula (III) (B = -O-) in the following way:



(V)

wherein m_1 is an integer from 1 to 6, preferably from 1 to 3; R_a and R_b, equal or different from each other, are as above defined;

when t = 0, u = 1 and m_0 = 1 the meanings of the various substituents are as above defined;

when t = 1, u = 0 and m_0 = 0 the meanings of the various substituents are as above defined and

C_{16} is bound, optionally by a bridging group -O-, to an aromatic radical or an alkyl-aril radical, where the aryl can be substituted, preferably with halogens, preferably with Cl, F; said aryl radical can also contain heteroatoms, such as O, N; the alkyl of the alkyl-aril radical is an aliphatic chain from 1 to 3 carbon atoms, preferably $-CH_2-$;

X_1 of formula A $-X_1-$ NO_2 is a bivalent connecting bridge, chosen from the following:

- Y

Y is a linear or whenever possible branched C1-C20 alkylene oxygen terminated, preferably having from 2 to 5 carbon atoms or is a C5-C7 cycloalkylene oxygen terminated optionally substituted;

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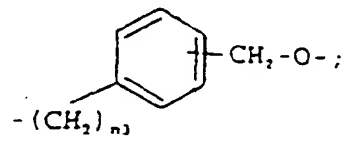

where n_3 is an integer from 0 to 3;

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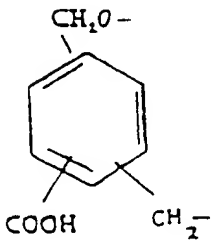

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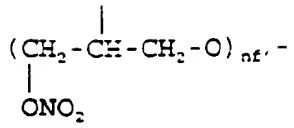

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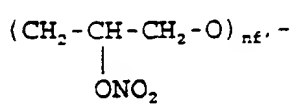

where nf' is an integer from 1 to 6, preferably fron 2 to 4;

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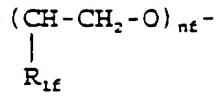


where R_{1f} = H, CH_3 and nf is an integer from 1 to 6, preferably from 2 to 4.

When in formula (II) t = 1 u = 0 and in formula (III) m_0 = 1, the preferred prostaglandin residues R are the following:

when B is O= (keto group with C_9); R_7, R_8, R_9 and R_{10} are such as to give a double bond between C_{13} and C_{14}; R_2 is OH; R_{27} is CH_3; the substituents of the carbon atoms of the C_2-C_7 and C_{16}-C_{19} aliphatic chains are H; R thus defined is known as the residue of Prostaglandin E_1;

or, by putting in the formula of Prostaglandin E_1 R_1 = CH_3 and

R_3, R_4, R_5, R_6 such as to give a double bond between C_5 and C_6; R thus defined it is known as the residue of Arbaprostil;

or, by putting in the formula of Arbaprostil $R_7 = R_8 = R_9 = R_{10} = H$; R_1 and R_2 are such as to form the group C=O with C_{15}; B is OH; $R_{27} = C_3H_7$, R thus defined it is known as the residue of Unoprostone;

or, by putting in the formula of Arbaprostil $R_{11} = R_{12} = CH_3$; $R_1 = H$, R thus defined it is known as the residue of Trimoprostil;

or, when in the formula of Arbaprostil B is OH; $R_1 = H$; R thus defined it is known as the residue of Prostaglandin $F_{2\alpha}$;

or, when in the formula of Prostaglandin $F_{2\alpha}$ B is O= (keto group with C_9), R thus defined it is known as the residue of Prostaglandin E_2;

or, when in the formula of Arbaprostil B is OH; R thus defined it is known as the residue of Carboprost;

or, by putting in the formula of Arbaprostil $R_1 = H$; $R_{17} = H$; $R_{19} = CH_3$; $R_3 = R_4 = R_5 = R_6 = H$; $R_{27} = C_2H_5$; $R_{13} = R_{16} = H$ and $R_{14} = R_{15}$ being free valences such as to form a double bond between C2 and C3; R thus defined it is known as the residue of Limaprost;

or, by putting in the formula of Trimoprostil $R_3 = R_4 = R_5 = R_6 = H$ and positioning the double bond between C_2 and C_3 instead that between C_5 and C_6; R thus defined it is known as the residue of Gemeprost;

or, by putting in the formula of Arbaprostil $R_1 = R_2 = H$; $R_{12} = OH$; $R_{11} = CH_3$; $R_3 = R_5 = R_4 = R_6 = H$; R thus defined it is

known as the residue of Misoprost;

or, by putting in the formula of Arbaprostil R_1 = H; R_{18} = CH_3; R_{27} = C_2H_5; R_3 and R_4 are such that one of them is a free valence and the other is a single bond with an oxygen atom so so that together with the carbon atom C_6 they form a keto group C=O; R5 = R6 = H; R thus defined it is known as the residue of Ornoprostil;

or, as in Arbaprostil, without the C_7-C_2 aliphatic chain and the carbon atoms C_9-C_8 being linked to the group of formula (IV) as shown in (V); R_1 = H; R_{11} = CH_3; R_{21}, R_{22}, R_{23} and R_{24} being each a free valence so to form a triple bond between C_{18} and C_{19}; R thus defined it is known as the residue of Beraprost;

when t = 0; u = 1 and m_o = 1: R_a = R_b = H and R is the residue of Misoprostol; R thus defined it is known as the residue of Rioprostil;

when t = 1, u = 0 and m_o = 0:

when R is the residue of Arbaprostil except that R_1 = H, R_{19} or R_{20} is a free valence or is H, so that between C_4 and C_5 there is a double bond; C_{16} is linked to a group -O-A_r wherein A_r = phenyl; R thus defined it is known as the residue of Enprostil;

when R is the residue of Arbaprostil except that B is OH; R_1 = H; C_{16} is linked to a group -CH_2-A_r where A_r is phenyl; it is defined a radical known as the residue of Latanaprost;

or, when in the formula of Enprostil R_{20} = R_{19} = H; it is defined a radical known as the residue of Sulprostone.

The products of the invention are obtained starting from the precursors in which R is as above defined and containing at least one carboxylic function, usually at position 2 of the corresponding formula (III); in the case of Beraprost the function -COOH is in the residue of formula (IV).

When the precursor has no free function -COOH, reactions to obtain it which are well known in the art are performed, for example by reaction of an esther or by oxidation of an alcohol.

The above substances may already exist as such (e.g. Arbaprostil, Prostaglandin E_1, Rioprostil, as described above).

For the precursors described in the literature, which have the carboxylic function substituted in various ways, in order to perform the synthesis according to the present invention it is preferable to start from the corresponding precursors in the acid form, i.e. bearing e free carboxylic group.

In particular, as preferred precursors one may mention Prostaglandin E_1, Arbaprostil, Unoprostone, Trimoprostil, Prostaglandin $F_{2\alpha}$, Prostaglandin E_2, Carboprost, Limaprost, Misoprostol, Gemeprost, Latanoprost, Ornoprostil, Beraprost, Enprostil, Rioprostil, Sulpostrone. These substances are prepared according to the methods described in "The Merck Index", Ed. 12, herein fully incorporated by reference.

The products of the present invention having the general formula

$A-X_1-NO_2$

with the connecting bridge X_1 as above defined, are obtainable by using the methods of the known art described, for example, in WO 92/01668 and WO 95/30641, herein fully incorporated by reference. In general, the connection between A and X_1 is of the ester -C(O)O- type or amide -C(O)NH- or -C(O)N(R_{1c})- type, as defined in X of formula (II) above, and can be obtained by using known synthetic routes.

The most direct synthetic route includes reaction of acyl chlorides R-CO-Cl in halogen alcohols of the type HO-Y-Cl, HO-Y-Br, HO-Y-I, Y being X_1 without oxygen, in experimental conditions which are part of the known art.

The reaction products of formula R-CO-O-Y-Cl (Br, I) can also be obtained by reaction of the sodium or potassium salts of said acids RCOOH with dihalogen derivatives of the general formula YCl_2, YBr_2 or YI_2.

The reaction products are converted into the final products by reaction with $AgNO_3$, in acetonitrile, according to the known methods of literature.

The general scheme is as follows:

$R-CO-Cl + HO-Y-Br \rightarrow R-CO-O-Y-Br + AgNO_3 \rightarrow A-X_1NO_2$

where X_1 = YO.

Another general scheme is as follows:

$R-CO-ONa + Br_2Y \rightarrow R-CO-O-Y-Br + AgNO_3 \rightarrow A-X_1NO_2$

where X_1 = YO.

In the case of amides, the synthetic sequence includes reaction of the same acyl chlorides RCOCl with aminoalcohols

of the general formula:

$$NH_2\text{-}Y\text{-}OH,\ NHR_{1c}\text{-}Y\text{-}OH$$

to give amides of the general formula:

$$R\text{-}CO\text{-}NH\text{-}Y\text{-}OH \text{ and } R\text{-}CO\text{-}NR_{1c}\text{-}Y\text{-}OH$$

according to known methods.

The reaction of these amides with halogenating agents such as, for example, PCl_5, PBr_3, $SOCl_2$, and others, leads to halogen derivatives of the general formula:

$$R\text{-}CO\text{-}NH\text{-}Y\text{-}Br(Cl) \text{ and } R\text{-}CO\text{-}NR_{1c}\text{-}Y\text{-}Br(Cl).$$

By reaction with $AgNO_3$ in acetonitrile according to methods reported in the literature, are obtained the final products $A\text{-}X_1\text{-}NO_2$.

The sequence of the reaction can be schematised as follows:

$$R\text{-}CO\text{-}Cl + NHR_{1c}\text{-}Y\text{-}OH \longrightarrow R\text{-}CO\text{-}NR_{1c}Y\text{-}OH \xrightarrow{PCl_5}$$

$$R\text{-}CO\text{-}NR_{1c}\text{-}Y\text{-}Br + AgNO_3 \longrightarrow R\text{-}CO\text{-}NR_{1c}\text{-}Y\text{-}ONO_2$$

where YO is X_1.

An alternative route to formation of the esters is reaction of the sodium or potassium salts of the acids with the nitric esters of halogen alcohols of the general formula:

$$NO_2\text{-}O\text{-}Y\text{-}Cl(Br,I)$$

to directly give the products of the invention.

The reaction scheme is as follows:

$$R\text{-}CO\text{-}ONa + Br\text{-}Y\text{-}ONO_2 \longrightarrow R\text{-}CO\text{-}O\text{-}Y\text{-}ONO_2$$

where YO is X_1.

According to a further process for the preparation of the

compounds of the invention the acid derivatives RCOOH are reacted with alcohols containing in the molecule a group $-ONO_2$ in the presence of aromatic sulphochlorides, in the presence of bases, such as trialkylamine, which neutralize the HCl released by the reaction.

Can also be used synthetic routes similar to those described above, where the di-halogen derivative Br_2Y is reacted with -ONa. The reaction products are then converted into acetonitrile by reaction with $AgNO_3$ according to the above shownreactions.

The general scheme is shown below

$$-O\ Na + Br_2Y \longrightarrow O\text{-}Y\text{-}Br \xrightarrow{AgNO_3} -O\text{-}Y\text{-}ONO_2$$

In addition to being used in the treatment of male impotence as explained at the beginning, the products of the invention can also be used in the known therapeutic applications of drugs containing prostaglandins as the active ingredient, such as in the treatment of cerebrovascular and cardiovascular disorders, glaucoma, peptic ulcer and as abortifacients

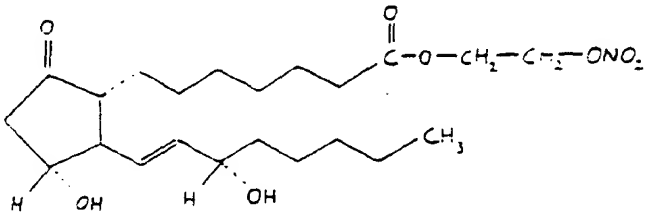
In particular, the derivatives of Prostaglandin E_1 are preferred.

Following treatment of experimental animals with the new substances, no hypotension reactions nor the algogenic activity possessed by prostaglandins were observed. In fact, differently from PGE_1, the new derivatives of the invention were inactive in pain-induction tests.

The examples below explain the purpose of the invention and should not be understood as a limitation of same.

Example 1

Synthesis of 2-nitroxyethyl ester of prostaglandin E_1



19,1 mg (0,0539 mmoles) of PGE_1 was dissolved in 0,7 ml of absolute acetone in a 5-ml flask. 11,5 mg(0,0604 mmol) of p-toluenesulphochloride, 12 mg(0,01188 mmoles) of triethylamine and 8 mg(0,0748 mmoles) of 2-nitroethanol were then added to the solution. The flask was closed and the reaction mixture was stirred for 22 hours at room temperature. At the end the solvent was evaporated off under vacuum, the residue was treated with 3 ml of water and the mixture was extracted with ethyl acetate three times using 7 ml each time.

The pooled organic extracts were washed with 1 ml of water and then 1,5 ml of a saturated NaCl solution. After drying over sodium sulphate, they were evaporated off to dryness under vacuum.

The oily residue which was obtained was dissolved in the lowest amount of dichloromethane and chromatographed using a small column packed with 4 g of silica gel (Silica Gel 60 A, 230-400 mesh). Dichloromethane was used as the initial eluant followed by a mixture of dichloromethane and ethyl acetate

which was gradually enriched with the second component up to eluting with pure ethyl acetate. The column was then eluted with a mixture of ethylacetate/methanol, gradually enriched with methanol, up to using the pure alcohol. The fractions were analysed by TLC on silica gel (Silica Gel 60 F_{254}), using the eluting mixture ethyl-acetate/acetic-acid 20/0,5. The test tubes containing the reaction product were those containing the eluates with pure ethyl acetate. Said eluates were joined together and the solvent was evaporated off to obtain 6 mg of a colourless oil (yield 25%) having an Rf in the above TLC elution system equal to 0,38. The ^1H NMR spectrum (CD_3OD) shows all signals corresponding to PGE_1 (ppm): 5,6 (m, 2H), 4-4,2(m,2H), 2,6-2,8(quartet, 1H), 2,0-2,4(m), 1,2-1,8(m). Furthermore, two multiplets centred at δ = 4,75(2H) and δ = 4,4(2H) respectively, corresponding to the two methylene groups of 2-nitroethanol esterified with the carboxylic group of PGE_1, were observed.

I.R. spectrum: 3382 cm^{-1}(OH), 2858-2930 cm^{-1} (-CH-, $-CH_2$, $-CH_3$-), 1774 cm^{-1}(C = O ester), 1773 cm^{-1}(group C = O in a five atom ring), 1634 and 1280 cm^{-1}($-O-NO_2$).

12,4 mg (65% of the starting amount) of unreacted PGE_1 was recovered from the chromatographic fractions eluted with the ethylacetate/methanol mixture.

Pharmacological tests

In the pharmacological tests, the products were administered to animals by local injection in a physiological solution.

The control groups were treated with a physiological solution.

Prostaglandin E_1, sodium nitroprusside and SIN-1, chemically defined as 3-(4-morpholinyl)sydnone imine, which is the active metabolite of molsidomine, were used as reference products.

Example 2

Relaxing effect in vitro on isolated human cavernosus artery and cavernosus corpus.

The method described by Hempelmann R.G. et al., European Journal of Pharmacology, 1995,276, 277-280, was followed using erectile tissues from patients subjected to surgery.

The cavernosus arteries were isolated and cleaned of the surrounding connective tissue. Segments about 2-mm long were obtained and mounted in a myograph.

After building a diameter/tension curve, the artery segments were adjusted to a diameter corresponding to 90% of that reached in the presence of a trasluminal pressure of 100 mmHg. After a stabilisation period of about 60 minutes, a contraction was induced by the addition of 3×10^{-6}M adrenaline. After 15 minutes, the test compounds were administered at a concentration of 10^{-6}M and the per-cent relaxation induced by the administration of the test product was recorded for each. The results are shown in Table 1.

Another set of experiments was conducted according to the same methodology, using isolated strips of cavernous tissue about 3×3×5 mm in size suspended isometrically, with

application of a 5-10 mN tension in baths for isolated organs. The results are shown in Table 2.

In both experimental models an inhibitory effect of the adrenalin-induced contraction following either treatment with PGE_1 or administration of the nitric-acid-donor SIN-1 was found. The PGE_1 derivative according to the present invention is shown in the tables by the abbreviation $NO\text{-}PGE_1$.

This compound showed an effect superior to both native prostaglandin and SIN-1.

Table 1: Inhibitory effect of some derivatives on isolated human cavernosus artery pre-contracted with 3×10^{-6} M adrenalin (for each treatment group n = 5 replications)

Treatment	inhibition of contraction (%)
10^{-6}M PGE_1	19±4
10^{-6}M SIN-1	36±7
10^{-6}M $NO\text{-}PGE_1$	41±9

Table 2: Inhibitory effect of some derivatives on isolated human cavernosus tissue pre-contracted with 3×10^{-6} M adrenaline (for each treatment group n = 4)

Treatment	inhibition of contraction (%)
10^{-6}M PGE_1	52±5
3×10^{-6}M SIN-1	41±6
10^{-6}M $NO\text{-}PGE_1$	71±6

Example 3

Evaluation of induced erection activity and of hypotensive effect in rats.

The method described by Pineiro et al., European Urology 1993, 24, 492-499, was used. Male rats weighing about 350 g (5 animals/group) were anaesthetised with urethane and maintained at a temperature of 37°C throughout the test. The cavernosus corpuses were exteriorized by perineal section. The right cavernosus corpus was connected to a pressure transducer using a heparinised catheter and the left one was connected using a PE-10 plastic tube to a syringe by which the products were administered.

The right carotide artery was cannulated and connected to a pressure transducer to measure the systemic blood pressure. The products were administrated intracavernously at a volume of 0,03 ml at a 10^{-3}M concentration and the intracavernous pressure and systemic blood pressure were monitored. The results given in Table 3 show that PGE_1 was slightly active in this model, while sodium nitroprusside induced a remarkable erection activity. Both derivatives caused a drop in systemic blood pressure, which was particularly marked in the case of nitroprusside. NO-PGE_1 showed an effect superior to both PGE_1 and sodium nitroprusside on intracavernous pressure, while causing a non significant drop in systemic blood pressure, which was comparable to that of starting Prostaglandin, and was significantly lower than that of nitroprusside.

As a result, the products of the invention have been shown to possess a pharmacodynamic profile which is more favourable compared to the reference compounds.

Table 3: Effect of intracavernosus treatment of various

derivatives on intracavernosus pressure (P) and systematic blood pressure (P) in anaesthetised rats (n=4)

Treatment	Increase in intracavernous P	Drop in systemic P (cm H_2O)
10^{-3}M sodium nitroprusside	27±3,7	51±7,8
10^{-3}M PGE_1	0,7±0,4	18,2±2,2
10^{-3}M NO-PGE_1	36±1,4	9,1±3,1

Example 4

Induced erection activity in rabbits

The method described by Stackl W. et al., Urological Research 1988, 455-458, was used. Male rabbits weighing about 2 Kg (n. 6 animals/group) were injected 1 ml of physiological solution containing 20μg of the test products into the right cavernosus corpus. During the injection, complete penis protrusion was observed, which was considered as 100% erection.

After injection, at pre-determined time intervals (0,5, 1,2 and 3 hours), the animals were observed for the presence of erection and evaluation of the relevant per-cent extent according to the following scheme:

0%=penis not visible

25%=glans visible

50%=penis protrusion equal to about half the complete lenght

75%=penis protrusion not complete, but greater than half the lenght

100%=complete penis protrusion

The results are given in Table 4 and show that the compound of the invention had a superior activity to that of the reference compound.

Table 4: Average per-cent values of extent of erection observed at different time intervals after intracavernosus administration of PGE_1 derivatives in rabbits

Treatement	n	30 minutes	1 hour	2 hours	3 hours
Controls 4	6	0%	0%	0%	
PGE_1 20 µg	6	13%	4%	0%	0%
NO-PGE_1 20 µg	6	92%	79%	67%	46%

EXAMPLE 5

Effect on painful response of the compound of the invention in rats

The conventional method of Randall-Selitto modified as described by Duarte I.D. G. et al., European Journal of Pharmacology, 1990, 186, 289-293, was used to determine the potential activity on painful response of the compound. The test includes the application of a steady 20-mmHg pressure to a back paw of rats. Pressure application was discontinued when the animals appeared to react and the response latency time, which was the parameter used to evaluate the analgesic or hyperalgesic effect of the test product, was recorded. Immediately after, the product was administered by the intradermal route in the subplantar area (administration volume 2,5 µl containing 0,1 µg of the test product). The test

was repeated 3 hours later.

The results given in Table 5 show that PGE_1 reduced the latency time, i.e. acted as a hyperalgesic agent. Sodium nitroprusside caused a slight nonsignificant increase in latency time. NO-PGE_1 was inactive, thus showing that the NO group in the PGE_1 molecule reduced the hyperalgesic property. In the table, the column identified by an "n" shows the number of animals used for each treatment.

Table 5: Effect of the compound of invention and reference substances on modified Randal-Selitto test

Product (μg/paw)	n	reaction time change (seconds)
PGE_1 (0,1)	8	-17±2
Sodium nitroprusside (5)	8	+4±2
NO-PGE_1 (0,1)	10	0

The derivatives were active in various tests useful to evaluate the potential pharmacological induced-erection activity versus reference compounds.

Unlike sodium nitroprusside, the invention compounds induced no hypotension at the pharmacologically active doses in the experimental impotency models.

The invention compounds showed no pain effects which could be found after the administration of PGE_1 in experimental tests in rats.

CLAIMS

1. Compounds, or their compositions, of the general formula:

$$A\text{-}X_1\text{-}NO_2 \quad (I)$$

for use as medicaments, in particular as drugs for the treatment of impotence, wherein:

$$A = R(CR_aR_bO)_u(COX)_t \quad (II)$$

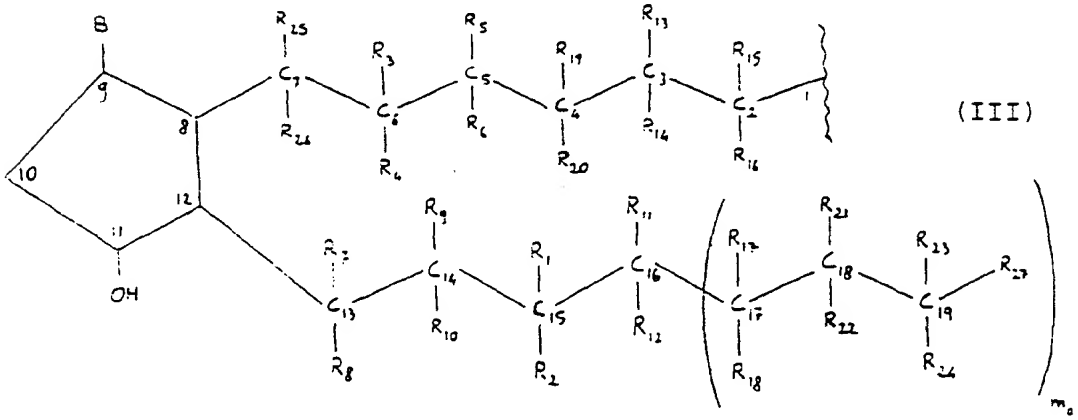
wherein:

t and u are integers and are equal to 0 or 1;

X = O, NH, NR_{1c} wherein R_{1c} is a linear or branched alkyl having from 1 to 10 carbon atoms;

R_a and R_b, equal or different from each other, are H, C_1-C_3 alkyl;

R is a radical having the following formula:



(III)

where m_o is an integer and can have a value of 0 or 1;

where the meaning of the various substituents of formula III is as it follows :

<u>when t = 1, u = 0 and m_o = 1</u>:

R_1 = H; an alkyl having from 1 to 6 carbon atoms, preferably from 1 to 3, or a free valence;

R_2 = OH, O- such as to form with R_1, when R_1 is a free valence, and with the carbon atom at position 15, a group C=O;

R_3, R_4, equal or different one from the other, are equal to R_1; or one of them is a bond O-, and the other is a free valence so that with the carbon atom C_5 they form a group C=O;

R_5, R_6, equal or different one from the other, are equal to R_1; when both R_5 and R_3 are each a free valence, R_5 and R_3 form a double bond between C_5 and C_6;

R_7, R_8, R_9, R_{10}, equal or different one from the other, have the same meaning of R_1; when R_7 or R_9, and at the same time R_8 or R_{10} are each a free valence, there is a double bond between C_{13} and C_{14};

R_{11} = R_1;

R_{12} = R_{11} or OH;

R_{13}, R_{14}, R_{15}, R_{16}, equal or different one from the other, are equal to R_1; when R_{13} or R_{15}, and at the same time R_{14} or R_{16}, are each a free valence, there is a double bond between C_3 and C_2;

R_{17}, R_{18}, equal or different one from the other, are equal to R_1;

R_{19}, R_{20}, equal or different one from the other, are equal to R_1; when R_6 or R_5 is a free valence, and R_{19} or R_{20} is a free valence, there is a double bond between C_4 and C_5;

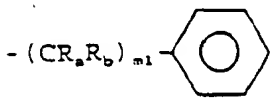
R_{21}, R_{22}, R_{23}, R_{24}, equal or different one from the other, are equal to R_1;

R_{25}, R_{26}, equal or different one from the other, are equal to R_1, but both $_{25}$ and R_{26} cannot be a free valence;

R_{27} is a linear or branched alkyl having from one to six carbon atoms;

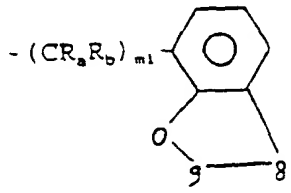
B is equal to the group O= (a keto group with the carbon atom at position 9 of the prostaglandin molecule) or is OH, or -O-;

when no aliphatic chain C_7-C_2 is at position 8, in its place there is the alkylaromatic residue:



(IV)

wich is bound to formula (III) (B = -O-) in the following way:



(V)

wherein m_1 is an integer from 1 to 6, preferably from 1 to 3;

R_a and R_b, equal or different from each other, are as above defined;

when t = 0, u = 1 and m_1 = 1 the meanings of the various substituents are as above defined;

when t = 1, u = 0 and m_1 = 0 the meanings of the various substituents are as above defined and

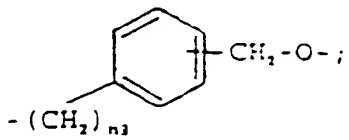
C_{16} is bound, optionally by a bridging group -O-, to an

aromatic radical or an alkyl-aril radical, where the aryl can be substituted, preferably with halogens, preferably with Cl, F; said aryl radical can also contain heteroatoms, such as O, N; the alkyl of the alkyl-aril radical is an aliphatic chain from 1 to 3 carbon atoms, preferably $-CH_2-$;

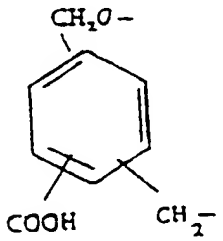
X_1 of formula A $-X_1-NO_2$ is a bivalent connecting bridge, chosen from the following:

- Y

Y is a linear or whenever possible branched C1-C20 alkylene oxygen terminated, preferably having from 2 to 5 carbon atoms or is a C5-C7 cycloalkylene oxygen terminated optionally substituted;

- 

where n_3 is an integer from 0 to 3;

- 

- $(CH_2-CH(ONO_2)-CH_2-O)_{nf}$-

- -$(CH_2-CH(ONO_2)-CH_2-O)_{nf}$-

where nf' is an integer from 1 to 6, preferably from 2 to 4;

- $-(CH(R_{1f})-CH_2-O)_{nf}-$

where R_{1f} = H, CH_3 and nf is an integer from 1 to 6, preferably from 2 to 4.

2. Compounds according to claim 1 wherein the prostaglandin residues R are the following:

when in formula (II) t = 1 u = 0 and in formula (III) m_o=1:

B is O= (keto group with C_9); R_7, R_8, R_9 and R_{10} are such as to give a double bond between C_{13} and C_{14}; R_2 is OH; R_{27} is CH_3; the substituents of the carbon atoms of the C_2-C_7 and C_{16}-C_{19} aliphatic chains are H; R thus defined is known as the residue of Prostaglandin E_1;

or, by putting in the formula of Prostaglandin E_1, R_1 = CH_3 and R_3, R_4, R_5, R_6 such as to give a double bond between C_5 and C_6; R thus defined is known as the residue of Arbaprostil;

or, by putting in the formula of Arbaprostil R_7 = R_8 = R_9 = R_{10} = H; R_1 and R_2 are such as to form the group C=O with C_{15}; B is OH; R_{27} = C_3H_7; R thus defined is known as the residue of Unoprostone;

or, by putting in the formula of Arbaprostil R_{11} = R_{12} = CH_3, R_1 = H, R thus defined s known as the residue of Trimoprostil;

or, when in the formula of Arbaprostil B is OH; R_1 = H;

R thus defined is known as the residue of Prostaglandin $F_{2\alpha}$;

or, when in the formula of Prostaglandin $F_{2\alpha}$ B is O= (keto group with C_9); R thus defined is known as the residue of Prostaglandin E_2;

or, when in the formula of Arbaprostil B is OH; R thus defined is known as the residue of Carboprost;

or, by putting in the formula of Arbaprostil R_1 = H; R_{17} = H; R_{19} = CH_3; R_3 = R_4 = R_5 = R_6 = H; R_{27} = C_2H_5; R_{13} = R_{16} = H and R_{14} = R_{15} being free valences such as to form a double bond between C_2 and C_3; R thus defined is known as the residue of Limaprost;

or, by putting in the formula of Trimoprostil R_3 = R_4 = R_5 = R_6 = H, and positioning the double bond between C_2 and C_3 instead that between C_5 and C_6; R thus defined is known as the residue of Gemeprost;

or, by putting in the formula of Arbaprostil R_1 = R_2 = H; R_{12} = OH; R_{11} = CH_3, R_3 = R_5 = R_4 = R_6 = H; R thus defined is known as the residue of Misoprost;

or, by putting in the formula of Arbaprostil R_1 = H; R_{16} = CH_3; R_{27} = C_2H_5; R_3 and R_4 are such that one of them is a free valence and the other is a single bond with an oxygen atom so that together with the carbon atom C_6 form a keto group C=O; R5 = R6 = H, R thus defined is known as the residue of Ornoprostil;

or, as in Arbaprostil, without the C_7-C_2 aliphatic chain and the carbon atoms C_9-C_8 linked to the group of formula

(IV) as shown in (V); R_1 = H; R_{11} = CH_3; R_{21}, R_{22}, R_{23}, R_{24} being each a free valence to form a triple bond between C_{18} and C_{19}; R thus defined is known as the residue of Beraprost;

when t = 0; u = 1 and m_o = 1 : R_a = R_b = H and R is the residue of Miscprostol, R thus defined is known as the residue of Rioprostil.

when t = 1, u = 0 and m_o = 0:

when R is the residue of Arbaprostil except that R_1 = H; R_{19} or R_{20} is a free valence or H, so that between C_4 and C_5 there is a double bond; C_{16} is linked to a group -O-A_r wherein A_r = phenyl; R thus defined is known as the residue of Enprostil;

when R is the residue of Arbaprostil except that B is OH; R_1 = H; C_{16} is linked to a group -CH_2-A_r where A_r is phenyl; it is defined a radical known as the residue of Latanaprost;

when in the formula of Enprostil R_{20} = R_{19} = H; it is defined a radical known as the residue of Sulprostone.

3. Compounds according to claims 1 and 2 used for the preparation of pharmaceutical compositions such as compositions for the treatment of impotence.

4. Compounds of the general formula (I) A-X_1-NO_2 according to claims 1 and 2.

5. Compounds according to claims 1 and 2 used for the preparation of pharmaceutical compositions such as compositions for the treatment of cerebrovascular and

cardiovascular disorders, glaucoma, peptic ulcer and as abortifacients.

6. Compounds according to claims 1 through 5 where R is the residue of Prostaglandin E_1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/03645

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C405/00 //A61K31/557

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 357 581 A (AMSU LTD) 7 March 1990 see claims	
Y	WO 94 10141 A (ALLERGAN INC) 11 May 1994 see claims	1-6
Y	WO 95 30641 A (NICOX LTD ;DEL SOLDATO PIERO (IT); SANNICOLO FRANCESCO (IT)) 16 November 1995 cited in the application see claims	1-6
A	US 5 625 083 A (BEZUGLOV VLADIMIR V ET AL) 29 April 1997 see claims	1-6
A	WO 94 06433 A (ALLERGAN INC) 31 March 1994 see claims	1-6

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
16 November 1998	02/12/1998

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/03645

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 102 230 A (TEIJIN LTD) 7 March 1984 see claims 1,19	1-6

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 98/03645

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0357581 A	07-03-1990	SE	463851 B	04-02-1991
		AU	638414 B	01-07-1993
		AU	4199489 A	02-04-1990
		CA	1335346 A	25-04-1995
		DE	68907909 T	23-12-1993
		DK	36491 A	01-03-1991
		EP	0432199 A	19-06-1991
		ES	2055677 T	01-09-1994
		GR	90300093 T	27-09-1991
		IE	62587 B	08-02-1995
		JP	7091199 B	04-10-1995
		JP	4501707 T	26-03-1992
		NO	301046 B	08-09-1997
		SE	8803087 A	03-03-1990
		WO	9002545 A	22-03-1990
WO 9410141 A	11-05-1994	US	5328933 A	12-07-1994
WO 9530641 A	16-11-1995	IT	1269735 B	15-04-1997
		IT	1274609 B	18-07-1997
		AT	168986 T	15-08-1998
		AU	2215695 A	29-11-1995
		AU	678063 B	15-05-1997
		AU	7809294 A	01-05-1995
		BR	9407749 A	12-02-1997
		BR	9507634 A	23-09-1997
		CA	2173582 A	13-04-1995
		CA	2190087 A	16-11-1995
		DE	69412109 D	03-09-1998
		WO	9509831 A	13-04-1995
		EP	0722434 A	24-07-1996
		EP	0759899 A	05-03-1997
		ES	2120070 T	16-10-1998
		HU	74446 A	30-12-1996
		HU	75961 A	28-05-1997
		JP	9503214 T	31-03-1997
		JP	9512798 T	22-12-1997
		US	5700947 A	23-12-1997
		US	5780495 A	14-07-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 98/03645

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5625083 A	29-04-1997	NONE	
WO 9406433 A	31-03-1994	US 5352708 A	04-10-1994
		AU 676492 B	13-03-1997
		AU 4852693 A	12-04-1994
		CA 2144967 A	31-03-1994
		EP 0660716 A	05-07-1995
		JP 8501310 T	13-02-1996
		US 5607978 A	04-03-1997
		US 5688819 A	18-11-1997
EP 0102230 A	07-03-1984	JP 1041146 B	04-09-1989
		JP 1559181 C	16-05-1990
		JP 59231066 A	25-12-1984
		JP 1041147 B	04-09-1989
		JP 1559184 C	16-05-1990
		JP 60011461 A	21-01-1985
		JP 1041143 B	04-09-1989
		JP 1559168 C	16-05-1990
		JP 59036657 A	28-02-1984
		JP 1584897 C	31-10-1990
		JP 2010152 B	06-03-1990
		JP 59036658 A	28-02-1984
		US 4649156 A	10-03-1987